Proteins

Scientists manipulate and mimic proteins for use in creating solutions for medicine, sustainable energy, and more

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Los Alamos National Laboratory graduate student, Patricia Langan, changes the properties of a green fluorescent protein in order to create new fluorescent protein variants.

Overview of Research and Highlights

Scientists at Los Alamos apply a unique collection of tools and expertise to gain a comprehensive understanding of the structure and function of proteins as well as to manipulate and mimic proteins for use in research.

This knowledge can lead to a multitude of possibilities, such as enhancing cellulose degradation for biofuels based on understanding the enzymes that naturally degrade it (cellulases) or creating new therapeutics for tuberculosis patients.

Known as “machines of life,” proteins are large biological molecules that consist of one or more chains of amino acids. They are fundamental components of all living things, such as enzymes, hormones, and antibodies. Proteins perform a variety of functions in living organisms, from catalyzing metabolic reactions to replicating DNA to transporting molecules in and out of cells.

At Los Alamos, scientists are studying the three-dimensional structures of proteins to better understand how they work. Through imaging and crystallography, as well as sequence data and computational modeling, scientists can determine the precise arrangement of atoms, which is key to the function of the protein.

Los Alamos scientists are also well-known for their use of proteins as tools in research. Internationally recognized lab protocols were developed here, such as affinity reagent development (proteins that work like antibodies to bind to specific targets) and the GFP-reporter toolkit (proteins that glow to identify a correct fold).

Software Development and Modeling

- Developed SOLVE and RESOLVE and contributed to PHENIX, all of which are protein-structure-solving software packages. SOLVE automatically carries out all the steps of macromolecular structure determination, from scaling data to calculating an electron density map. RESOLVE, SOLVE’s sister

application, improves electron density maps by using a statistical approach to combine experimental x-ray diffraction data with information about the expected characteristics of an electron density map
- Performed large scale molecular simulations of molecular machines to identify new antibiotic targets. Such understanding could help scientists develop new antibiotics to battle “superbugs” such as MRSA (methicillin-resistant Staphylococcus aureus) infections, as well as engineered strains of anthrax and plague. Also performed the first structural study of an entire long non-coding RNA, a class of molecules that play key roles in cancer and epigenetics.

Technology Development

- Created a new strategy for vaccine development using mosaic proteins—proteins that represent the best consensus when working with highly variable pathogens such as HIV. Mosaic proteins were used to make an HIV vaccine that is currently in a Phase 1 human trial.
- Using mosaic proteins for other vaccines, such as one against the Ebola virus.
- Designed an optical biosensor that quickly detects protein toxins and other biological pathogens. Applications for this sensor include detecting biothreat agents, food inspection, and medical treatment (from early diagnosis of infection to disease screenings to diagnosing breast and other cancers).

Protein and Enzyme Engineering

- Developed the Green Fluorescent Protein Toolbox to help scientists understand and solve the mysteries of protein dysfunction, including misfolding, aggregation, and abnormal movement. Los Alamos scientist Geoff Waldo improved GFP’s flexibility, usability, reliability, and sensitivity by engineering it to have more desirable characteristics. Applications for GFP range from monitoring the expression level of a target protein to performing more effective drug discovery.
- Engineered (in collaboration with University of California–Davis and the U.S. Department of Agriculture’s Agricultural Research Service) grapevines that produce a hybrid antimicrobial protein that recognizes and blocks Xylella fastidiosa, a bacterium that causes Pierce’s Disease. This engineering approach may also protect other economically important plants from this bacterium, and a similar strategy could be used against a broad range of pathogen-induced plant and human diseases.
- Created CHAMPS—chimeric antimicrobial proteins—that can rapidly eliminate bacteria from infected sites in plants and humans. These proteins have a very low susceptibility to antibiotic resistance. CHAMPS applications include therapeutically treating human infections, protecting crops against disease, and countering biothreat agents.
- Collaborated with the University of Florida to create a thermostable enzyme that can capture carbon with much greater efficiency. Such an enzyme might serve as a biocatalyst for carbon sequestration and biofuel production. This enzyme could (1) reduce carbon emissions from coal- and gas-fired power plants and (2) play a valuable role in the production of algae-based biofuels.
- Engineered enzymes designed to be highly resistant to high pH and high temperatures while maintaining functionality. For example, Los Alamos scientists created a consensus green fluorescent protein whose subject enzymes did not

degrade (for more than 12 hours) after exposures greater than 80 degrees Celsius and pH greater than 10. Applications for such enzymes include pharmaceuticals, oil and gas, paper and pulp, and bioenergy.

Neutron and X-ray Scattering

- Used complementary neutron and x-ray scattering techniques to resolve molecular-scale structural details of human tau protein. This protein may play a role in the development of neurodegenerative diseases, such as Alzheimer's disease.

Therapeutics Development

- Developing mosaic proteins that may one day become the first viable vaccine that can protect humans from HIV, the virus that causes AIDS.
- Developing an automated pipeline to generate antibodies against human gene products without the use of animals. Traditional methods use to expose a specific gene's function is to take the protein it produces and generate specific antibodies (usually by vaccinating an animal, such as a mouse or rabbit). Instead of animals, Los Alamos scientists will use "antibody libraries" expressed in bacteria and bakers yeast. The ultimate goal of this project is to identify antibodies in the libraries that recognize each human protein. Such work will facilitate the understanding of human disease and provide likely targets for therapeutic intervention.

Capabilities

Bioinformatics and Analytics	Patrick Chain
Biophysical Chemistry	Ryszard Michalczyk
Computational Modeling	Sara Y. Del Valle
Genome Technologies	Tracy Erkkila
Molecular Recognition and Design	Andrew Bradbury
Protein Engineering	Geoff Waldo
Structural Biology	Tom Terwilliger

LANL Facilities and Resources

- Protein Crystallography Station: Scientists at this facility investigate the structure of proteins, biological polymers, and membranes. To conduct such investigations, scientists use a combination of x-ray and neutron crystallography, protein expression and purification, isotopic labeling, structural enzymology, enzyme kinetics, and molecular biology.
- High-Throughput Gene Cloning and Protein Production Facility: This facility serves the Tuberculosis Structural Genomics Consortium. Scientists here collaborate with various universities and other national laboratories to better-understand how proteins work, as these are considered the "machines of life."
- National Flow Cytometry Resource: For over 30 years LANL has been a leader in the development and use of flow cytometry. Flow cytometry is useful for the sorting and analysis of cells, and has been shown to greatly enhance some methods of recognition ligand development.

Partners

- SpatioTemporal Modeling Center: NIH-funded collaboration between Los Alamos and the University of New Mexico, with the Laboratory providing modeling expertise and technology development, particularly in the field of novel affinity reagents, and UNM providing cell biology expertise in IgE receptor signaling, modeling, and single molecule imaging.
- Phenix: based on an NIH-funded collaboration with LBNL, the University of Cambridge, and Duke University (www.phenix-online.org) is a comprehensive x-ray crystallography structure determination software package that includes SOLVE, RESOLVE, and many other powerful algorithms and that is used worldwide by macromolecular crystallographers.

Sponsors, Funding Sources, or Agencies

- Department of Energy's Office of Science
- Department of Defense, Defense Threat Reduction Agency
- National Institutes of Health

Awards

- 2010 R&D100 Award for Ultrasonic Biofuel Harvester
- 2010 Federal Consortium Award for Reagentless Optical Biosensor technology
- 2008 R&D100 Award for 3D Tracking Microscope
- 1998 R&D100 Award for SOLVE: Creating 3D Pictures of Protein Molecules